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# Enantioselective Synthesis of 4-Aminotetrahydroquinolines via 1,2-Reductive Dearomatization of Quinolines and Copper(I) Hydride-Catalyzed Asymmetric Hydroamination

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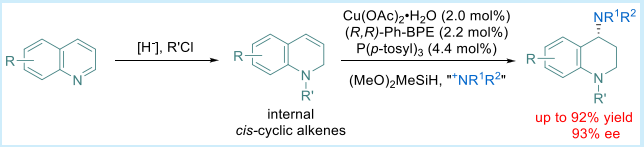
Supporting Information

**ABSTRACT:** A 1,2-reductive dearomatization of quinolines and copper(II) acetate monohydrate/(*R*,*R*)-Ph-BPE/P(*p*-tolyl)$_3$-catalyzed enantioselective hydroamination sequence was developed, affording diverse 4-amino-1,2,3,4-tetrahydroquinolines with high levels of enantioselectivity in either a stepwise or one-pot fashion. Pleasingly, internal *cis*-cyclic alkenes, which are challenging substrates in copper hydride-catalyzed enantioselective hydroamination reactions, were transformed efficiently under mild conditions.






Chiral tetrahydroquinolines (THQs) are widespread in pharmaceuticals and natural products (Figure 1a).[1] Their

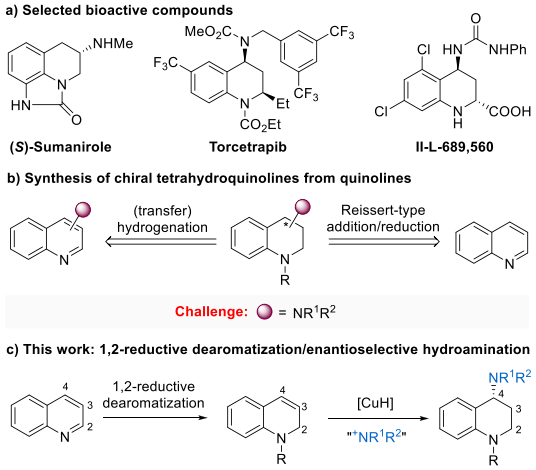



**Figure 1.** Synthesis of chiral 1,2,3,4-tetrahydroquinolines via dearomatization of quinolines.

efficient construction has long been a goal for both organic and medicinal chemists.[2] In addition to well-established cyclization reactions such as the Pavarov reaction,[1c] dearomatization of quinolines represents a straightforward and attractive method toward these scaffolds. Notable examples include asymmetric (transfer) hydrogenation and other reduction reactions (Figure 1b).[3] Despite considerable progress, the enantioselective incorporation of THQs with amine functionalities, which are also ubiquitous components in natural products and drug molecules, remains less explored.[3k−m,o] This might be attributed to the fact that the strong coordination and poisoning capacity of the substrates and reduced products lead to potential deactivation of the catalysts. In addition, installation of the amine moiety on the quinoline is required prior to the asymmetric transformation, which somehow renders this protocol impractical. Considering the significant importance of chiral amine-substituted THQs, as exemplified by 4-amino-1,2,3,4-tetrahydroquinolines, which show various biological activities, including CETP inhibition,[4] NMDA receptor antagonism,[5] and potent bradykinin antagonism,[6] the development of a straightforward approach directly starting from abundant quinolines is highly desirable.[7]

Reissert-type nucleophilic addition constitutes a commonly used strategy for direct functionalization of quinolines and offers a flexible choice to introduce functionalities such as nitrile, alkyne, and so on (Figure 1b).[8] However, to the best of our knowledge, the engagement of amine moieties is problematic and remains unknown to date. To circumvent the challenge, we envisioned that an umpolung tactic using electrophilic amines might be adopted. This hypothesis was inspired by pioneering studies by the Buchwald group[9a] and the Hirano and Miura groups,[9b] who seminally reported copper hydride-catalyzed enantioselective hydroamination reactions independently in 2013. Since then, a series of chiral amines were obtained in good to excellent yields, regioselectivities, and enantioselectivities from readily available alkenes and alkynes.[9−11] More recently, our group disclosed that this powerful copper catalysis could be extended to benzofurans, for which a benzofuran ring opening/enantioselective hydroamination cascade was observed.[9q] On the basis of the above considerations and continuing with our interest in value-added functionalization of aromatic com-

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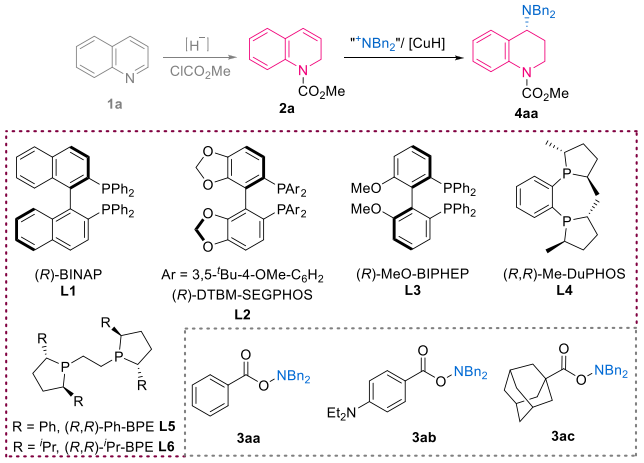
**Table 1. Optimization of the Reaction Conditions**[a]




| entry | ligand | conc. (M) | 3 | yield of **4aa** (%)[b] | ee of **4aa** (%)[c] |
|---|---|---|---|---|---|
| 1 | **L1** | 0.5 | **3aa** | 33 | 42 |
| 2 | **L2** | 0.5 | **3aa** | 72 | 18 |
| 3 | **L3** | 0.5 | **3aa** | 59 | 57 |
| 4 | **L4** | 0.5 | **3aa** | 6 | 14 |
| 5 | **L5** | 0.5 | **3aa** | 95 | 80 |
| 6 | **L6** | 0.5 | **3aa** | 20 | 12 |
| 7 | **L5** | 0.1 | **3aa** | 93 | 84 |
| 8 | **L5** | 0.02 | **3aa** | 32 | 84 |
| 9 | **L5** + $PPh_3$ | 0.1 | **3aa** | 78 | 86 |
| 10 | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3aa** | 83 | 87 |
| 11 | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3ab** | 85 | 87 |
| 12 | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3ac** | 85 | 87 |
| 13[d] | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3ac** | 87 | 88 |
| 14[d,e] | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3ac** | 94 | 88 |
| 15[d,e,f] | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3ac** | 88 | 89 |
| 16[d,e,f,g] | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3ac** | 92 | 90 |
| 17[d,e,f,h] | **L5** + P(*p*-tolyl)$_3$ | 0.1 | **3ac** | 75 | 87 |

[a]Reaction conditions: $Cu(OAc)_2$ (5 mol %), ligand (5.5 mol %), secondary ligand (11 mol %, if used), **2a** (0.20 mmol), **3** (0.24 mmol), and $(MeO)_2MeSiH$ (0.8 mmol) in THF at 40 °C for 20 h. Catalyst was preprepared by mixing $Cu(OAc)_2$, ligand and $(MeO)_2MeSiH$ together in THF. [b]Isolated yields. [c]Determined by SFC analysis. [d]1.4 equiv of **3ac** was used. [e]$Cu(OAc)_2{\cdot}H_2O$ was used instead of $Cu(OAc)_2$. [f]The reaction was carried out at room temperature. [g]$Cu(OAc)_2{\cdot}H_2O$ (2.0 mol %), **L5** (2.2 mol %), P(*p*-tolyl)$_3$ (4.4 mol %). [h]$Cu(OAc)_2{\cdot}H_2O$ (1.0 mol %), **L5** (1.1 mol %), P(*p*-tolyl)$_3$ (2.2 mol %), 48 h.

pounds, we explored whether copper hydride catalysis could provide a general solution toward the synthesis of challenging amine-substituted THQs with high enantioselective induction (Figure 1c). Herein we report our results from this study.

At the outset, we envisioned that enantioselective hydroamination of quinolinium salts might be directly enabled by copper hydride catalysis. However, the initial attempts all failed, along with the observation that the starting materials remained. This is largely due to the difficulties associated with resonance stabilization caused by aromaticity. Inspired by the elegant examples of stepwise reduction/enantioselective catalysis,[12] we therefore used a sequence as an alternative strategy, namely, 1,2-reductive dearomatization of quinolines followed by copper hydride-catalyzed asymmetric hydroamination of the resultant 1,2-dihydroquinolines. Nevertheless, this method would be very challenging since the internal *cis*-cyclic alkenes are well-known as challenging and problematic substrates in enantioselective hydroamination catalyzed by copper hydride.[11f]

Accordingly, *N*-protected 1,2-dihydroquinoline **2a**, synthesized from quinoline (**1a**) via 1,2-reductive dearomatization, was used as the substrate in the hydroamination reaction (Table 1). Upon treatment of **2a** with 1.2 equiv of hydroxylamine ester **3aa** in a THF solution of CuH catalyst (obtained from $Cu(OAc)_2$, (*R*)-BINAP, and $(MeO)_2MeSiH$, 0.5 M) at room temperature for 20 h, the desired product **4aa** was obtained in 33% yield with 42% ee (entry 1, Table 1). Encouragingly, after screening of various ligands, we found that utilization of (*R*,*R*)-Ph-BPE (**L5**) gave **4aa** in 95% yield with 80% ee (entry 5, Table 1). Slightly improved enantioselectivity was achieved when the substrate was diluted to a concentration of 0.1 M (84% ee; entry 7, Table 1), but further decreasing the concentration resulted in a poor yield (32%; entry 8, Table 1). Gratifyingly, the utilization of a secondary ligand[13] was found to be beneficial to the reaction, and P(*p*-tolyl)$_3$ provided the best results (87% ee; entry 10, Table 1). Notably, different dibenzylamine precursors (**3aa**–**ac**) exerted little impact on the reaction outcome (entries 11 and 12, Table 1). 1-Adamantyl acid-derived hydroxylamine ester **3ac** was chosen as the reaction partner because of its slightly improved efficiency and relatively ready availability and cheapness. Further investigations of the substrate ratio, copper source, reaction temperature, and catalyst loading were conducted (entries 13–17, Table 1). It was identified that the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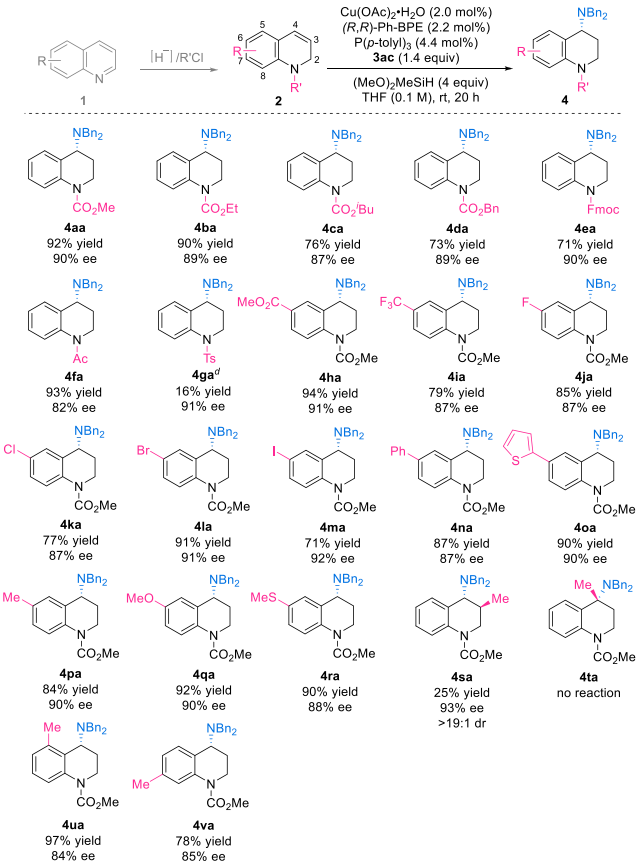
reaction of **2a** with **3ac** (1.4 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$ (2 mol %), (*R*,*R*)-Ph-BPE **L5** (2.2 mol %), $P(p\text{-tolyl})_3$ (4.4 mol %), and $(MeO)_2MeSiH$ (0.8 mmol) at room temperature gave the best results (92% yield, 90% ee; entry 16, Table 1).

With the optimized conditions in hand, we next explored the scope of 1,2-dihydroquinolines (Scheme 1). Various protecting

**Scheme 1. Investigation of 1,2-Dihydroquinolines**[a,b,c]

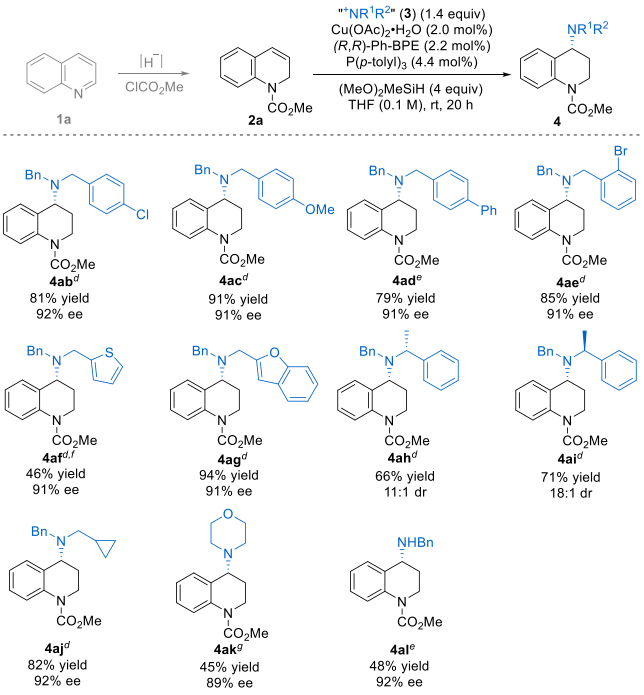



[a]Reaction conditions: as in entry 16 of Table 1. [b]Isolated yields are shown. [c]The ee values were determined by HPLC or SFC analysis. [d]20 h at rt and then 12 h at 40 °C.

groups on the nitrogen atom of the 1,2-dihydroquinoline, such as $-CO_2Me$, $-CO_2Et$, $-CO_2{}^iBu$, $-CO_2Bn$, Fmoc, and −Ac, were well-tolerated, and good to excellent yields (71−93%) and enantioselectivities (82−90% ee) were achieved (**4aa**−**fa**). However, the Ts group had a detrimental effect on the reactivity, leading merely to the observation of recovered substrate **2g** (16% yield, 91% ee; **4ga**). The reactions proceeded smoothly with 1,2-dihydroquinolines bearing different substituents at the 6-position ($-CO_2Me$, $-CF_3$, −F, −Cl, −Br, −I, −Ph, 2-thienyl, −Me, −OMe, −SMe), in all cases providing the corresponding THQs in good yields (71−94%) with excellent enantioselectivities (87−92% ee) regardless of their electronic properties (**4ha**−**ra**). Furthermore, substrates bearing a methyl substituent at other positions were evaluated (**4sa**−**va**). Low conversion was observed when the methyl group was incorporated at the 3-position (25% yield, 93% ee, >19:1 dr; **4sa**), while the reaction was inhibited with a methyl group at the 4-position. These decreased reactivities might be attributed to the unfavorable steric hindrance encountered in the hydrocupration step. It was remarkable to observe the formation of **4sa** in a highly enantioselective and diastereoselective fashion. As expected, 5- and 7-methyl substituted 1,2-dihydroquinolines were suitable substrates, leading to the isolation of **4ua** and **4va** in 97% yield with 84% ee and 78% yield with 85% ee, respectively.

Next, the amine electrophiles were examined. As illustrated in Scheme 2, various nitrogen sources bearing varied benzylic

**Scheme 2. Investigation of Amine Electrophiles**[a,b,c]




[a]Reaction conditions: as in entry 16 of Table 1. [b]Isolated yields are shown. [c]The ee values were determined by HPLC or SFC analysis. [d]4-(*N*,*N*-Diethylamino)benzoic acid-derived hydroxylamine ester was used. [e]1-Adamantanecarboxylic acid-derived hydroxylamine ester was used. [f]2.0 equiv of **3** was used. [g]Benzoic acid-derived hydroxylamine ester was used.

moieties ($4\text{-}ClC_6H_4CH_2-$, $4\text{-}MeOC_6H_4CH_2-$, $4\text{-}PhC_6H_4CH_2-$, $2\text{-}BrC_6H_4CH_2-$, 2-thienylmethyl, 2-benzofuranylmethyl) were well-accommodated, delivering the corresponding chiral tertiary amines (**4ab**−**ag**) in 46−94% yield with 91−92% ee. The reaction is also applicable to substrates **3h** and **3i** containing stereocenters adjacent to the nitrogen with opposite configuration. The two diastereoisomers **4ah** and **4ai** were obtained in 66% yield with 11:1 dr and in 71% yield with 18:1 dr, respectively, indicating that catalyst control process operates. Interestingly, the cyclopropane motif, which is of significance in drug discovery,[14] could be introduced through this hydroamination process (82% yield, 92% ee; **4aj**). The robustness of this reaction was further demonstrated by the successful incorporation of morpholine and benzylamine on THQs with excellent enantioselectivity (45% yield, 89% ee, **4ak**; 48% yield, 92% ee, **4al**).

Finally, we achieved the enantioselective construction of 4-amino-1,2,3,4-tetrahydroquinolines directly from quinolines in a one-pot fashion. However, the initial results were rather disappointing, leading to the isolation of **4aa** in 18% yield. With modified reaction conditions ($KBH_4$ was used for the 1,2-reduction of quinolines), the results were significantly improved, as shown in Scheme 3. The desired THQs were obtained in satisfactory yields (55−90%) with good enantioselectivities (87−90% ee). Notably, there is no need for isolation or



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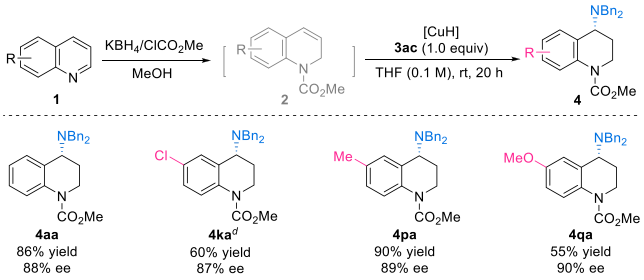
**Scheme 3. One-Pot Synthesis**[a,b,c]

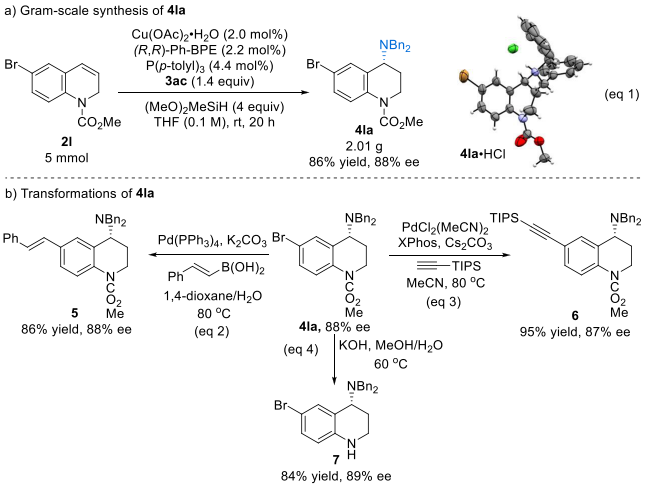



[a]Reaction conditions: **1** (0.5 mmol), $ClCO_2Me$ (0.6 mmol), and $KBH_4$ (0.5 mmol) were stirred at room temperature in MeOH (0.5 M) overnight. A solution of $Cu(OAc)_2·H_2O$ (4.0 mol %), **L5** (4.4 mol %), P(*p*-tolyl)$_3$ (8.8 mol %), $(MeO)_2MeSiH$ (1.0 mmol), and **3ac** (0.25 mmol) in THF (2.5 mL, 0.1 M) was added, and the reaction was continued at rt for 20 h. [b]Isolated yields are shown. [c]The ee values were determined by HPLC or SFC analysis. [d]3.0 equiv of **1** was used.

purification of the dihydroquinoline intermediate during the process.

To our delight, the protocol was also amenable to scale-up and diverse transformations. As shown in Scheme 4, the reaction of

**Scheme 4. Gram-Scale Synthesis and Transformations of 4la**




**2l** with **3ac** on a 5 mmol scale delivered **4la** in 86% yield (2.01 g) with 88% ee (eq 1). The absolute configuration of product **4la** was determined by X-ray crystallographic analysis of its enantiomeric pure hydrochloride salt (**4la**·HCl). Transformations of **4la**, including Suzuki coupling (eq 2) and Sonogashira coupling (eq 3), occurred smoothly to incorporate alkene and alkyne functionalities, respectively, on the THQ skeleton in high yields without any erosion of enantiopurity (86% yield, 88% ee, **5**; 95% yield, 87% ee, **6**). Besides, the $-CO_2Me$ group could be easily removed by treatment of **4la** with potassium hydroxide in a methanol/water mixture at 60 °C (84% yield, 89% ee; **7**) (eq 4). Importantly, the introduced functionalities such as alkene, alkyne, and N−H could offer easy handles for further modifications.

In conclusion, we have developed a 1,2-reductive dearomatization of quinolines and copper(II) acetate monohydrate/(*R*,*R*)-Ph-BPE/P(*p*-tolyl)$_3$-catalyzed enantioselective hydroamination sequence. Starting from readily available substituted quinolines, structurally diverse THQs bearing amine moieties were obtained in good to excellent yields with high enantioselectivities. Importantly, this method represents a rare example of highly enantioselective hydroamination of internal *cis*-cyclic alkenes. Compatibility with gram-scale reaction and versatile manipulations of the resultant THQs further enhance the synthetic utility of the current method.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02034.

Experimental procedures and analysis data for all new compounds (PDF)

### Accession Codes

CCDC 1903797 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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